AMENDMENTS TO THE CLAIMS

Please amend claims 1, 8, 16-18, 24, 25, 32, 39-41, 44, 45, and 47, as set forth below.

Please cancel claims 2, 15, 20, 26, 42, and 43.

The current listing of claims replaces all prior listings.

1. (Currently Amended) A method of generating a humanized mouse comprising recombining a first DNA construct with a second DNA construct,

wherein the first DNA construct has a mouse DNA sequence contained therein, and wherein the second DNA construct has a human DNA sequence contained therein ~~and the human DNA sequence is flanked by a first and second mouse DNA sequence that allows for recombination~~, wherein the first and second ~~mouse DNA sequences~~ constructs ~~are orthologous to and~~ have the same order and organization ~~orientation~~ relative to the human DNA sequences when ~~as human sequences flanking the human DNA sequence when it is~~ present in the genome of a human;

a) generating at least two recombinant chimeric ~~isolating an intermediate homologously recombined~~ DNA constructs comprising ~~having the~~ human and mouse DNA sequences ~~flanked by~~ of the first and second ~~mouse~~ DNA constructs, wherein each chimeric DNA construct comprises human DNA at one end of the chimeric DNA construct and mouse DNA at the other end of the chimeric DNA construct, and wherein a first chimeric DNA construct of the at least two recombinant chimeric DNA constructs comprises 5' regulatory DNA sequences and a second chimeric DNA construct of the at least two recombinant chimeric DNA constructs comprises 3' regulatory DNA sequences ~~and recombining the intermediate homologously recombined DNA construct with a third construct that has a mouse DNA sequence contained therein thereby generating a fourth DNA construct having a human sequence flanked by mouse sequences~~;

b) ligating the ends of the human DNA comprising the at least two chimeric DNA constructs;

c) recombining the ligated chimeric DNA constructs of step (b) with the second DNA construct to produce a third DNA construct, wherein the third DNA construct comprises

human sequences of the second DNA construct flanked by mouse sequences of the first DNA construct;

d) introducing the ~~recombined fourth~~ third DNA construct into a mouse embryogenic stem cell;

e) introducing the embryogenic stem cell of step (d) into an mouse blastocyst, thereby producing a chimeric blastocyst; and

f) implanting the chimeric blastocyst into a pseudopregnant mouse, wherein the pseudopregnant mouse delivers a humanized mouse, thereby generating a humanized mouse.

2. (Canceled)

3. (Original) The method of claim 1, wherein the first DNA construct is a bacterial artificial chromosome.

4. (Original) The method of claim 1, wherein the second DNA construct is a bacterial artificial chromosome.

5. (Original) The method of claim 4, wherein the bacterial artificial chromosome is linearized.

6. (Original) The method of claim 1, wherein the recombining is carried out in a strain of *E. coli*.

7. (Currently Amended) The method of claim [[1]]6, wherein the *E. coli* is deficient for *sbcB*, *sbcC*, *recB*, *recC* or *recD* activity and has a temperature sensitive mutation in *recA*.

8. (Currently Amended) The method of claim 1, wherein the human DNA sequence is selected from the group consisting of a G-protein coupled receptor gene, a kinase gene, a phosphatase gene, an ion channel gene, a nuclear receptor gene, an oncogene, a cancer suppressor gene, a viral receptor gene, a bacterial receptor gene, a P450 gene, an insulin receptor gene, an immunoglobin gene, a metabolic pathway gene, a transcription factor gene, [[,]] a cytokine gene, a cell signaling pathway gene and a cell cycle gene.

9. (Original) The method of claim 1, wherein the third DNA construct is a bacterial artificial chromosome.

10. (Original) The method of claim 1, wherein the human DNA sequence is a human gene sequence having at least one intron contained therein.

11. (Previously Presented) The method of claim 10, wherein the third DNA construct has a selection marker contained within the at least one intron.

12. (Original) The method of claim 11, wherein the selection marker is added following the recombining step.

13. (Original) The method of claim 11, wherein the selection marker is a positive selection marker.

14. (Previously Amended) The method of claim 11, wherein the third DNA construct has a second selection marker that flanks the first or the second mouse DNA sequence.

15. (Cancelled)

16. (Currently Amended) The method of claim 1, wherein the human DNA sequence of the first DNA chimeric construct comprises a coding sequence comprising a start codon having a 5' end, and wherein the ~~first~~ mouse DNA sequence of the first chimeric DNA construct ~~in the second construct~~ is joined to the human DNA coding sequence at the 5' end of the start codon.

17. (Currently Amended) The method of claim 16, wherein the human DNA sequence of the second chimeric DNA construct comprises a coding sequence comprising[[es]] a stop codon having a 3' end, and wherein the ~~second~~ mouse DNA sequence of the second chimeric DNA construct ~~in the second construct~~ is joined to the human DNA coding sequence at the 3' end of the stop codon.

18. (Currently Amended) A PCR assembled linearized bacterial artificial chromosome DNA construct for performing homologous recombination within a cell of a non-human animal, the construct comprising:

a human DNA coding sequence having at least one intron disposed therein;

a selection marker gene contained within said at least one intron;

a first non-human animal DNA sequence and a second non-human animal DNA sequence, wherein said first and second non-human animal DNA sequences flank the human DNA coding sequence,

wherein the first and second non-human animal DNA sequences are from the same species,

wherein the first and second non-human animal DNA sequences are orthologous to and have the same order and orientation relative to the human DNA sequence as human sequences flanking the human DNA sequence when it is present in the genome of a human.

19. (Original) The DNA construct of claim 18, further comprising a second selection marker adjacent to one of the non-human DNA sequences.

20. (Cancel)

21. (Original) The DNA construct of claim 18, wherein the first and second non-human DNA sequences are mouse genomic DNA sequences.

22. (Previously Presented) The DNA construct of claim 18, wherein the non-human animal DNA sequences are from about 0.1 to 200 kb in length.

23. (Previously Presented) The DNA construct of claim 18, wherein the human DNA comprises a coding sequence comprising a start codon having a 5'end and the first non-human sequence is joined adjacent to the 5' end of the start codon of the human DNA coding sequence.

24. (Currently Amended) The DNA construct of claim 23, wherein the human DNA coding sequence comprises ~~comprises~~ a stop codon having a 3' end, and the first non-human sequence is joined adjacent to the 3' end of the stop codon of the human DNA coding sequence.

25. (Currently Amended) A method for generating a DNA construct for performing homologous recombination within a cell by

recombining a first DNA construct with a second DNA construct, wherein the first DNA construct has a non-human animal DNA sequence contained therein,

wherein the second DNA construct has a human DNA sequence contained therein ~~and the human DNA sequence is flanked by a first and a second non-human animal DNA sequence~~,

wherein ~~the non-human animal DNA sequences of~~ the first and second construct ~~are from the same species,~~

~~wherein the first and second non-human animal DNA sequences are orthologous to and~~ have the same order and orientation relative to the human DNA sequence~~s as human sequences flanking the human DNA sequence~~ when ~~it is~~ present in the genome of a human; [[and]]

a) generating at least two recombinant chimeric DNA constructs comprising human and non-human animal DNA sequences of the first and second DNA constructs, wherein each chimeric DNA construct comprises human DNA at one end of the chimeric DNA construct and non-human animal DNA at the other end of the chimeric DNA construct, and wherein a first chimeric DNA construct of the at least two recombinant chimeric DNA constructs comprises 5' regulatory DNA sequences and a second chimeric DNA construct of the at least two recombinant chimeric DNA constructs comprises 3' regulatory DNA sequences;

b) ligating the ends of human DNA comprising the at least two chimeric DNA constructs;

c) recombining the ligated chimeric DNA constructs of step (b) with the second DNA construct to produce a third DNA construct, wherein the third DNA construct comprises human sequences of the second DNA construct flanked by non-human animal sequences of the first DNA construct; and

d) isolating the recombined third DNA construct of step (c) ~~a homologously recombined third DNA construct having the human DNA sequence flanked by the first and second non-human animal DNA sequence~~.

26. (Canceled)

27. (Original) The method of claim 25, wherein the first DNA construct is a bacterial artificial chromosome.

28. (Original) The method of claim 25, wherein the second DNA construct is a bacterial artificial chromosome.

29. (Original) The method of claim 28, wherein the bacterial artificial chromosome is linearized.

30. (Original) The method of claim 25, wherein the recombining is carried out in a strain of *E. coli*.

31. (Original) The method of claim 25, wherein the *E. coli* is deficient for *sbcB*, *sbcC*, *recB*, *recC* or *recD* activity and has a temperature sensitive mutation in *recA*.

32. (Currently Amended) The method of claim 25, wherein the human DNA sequence is selected from the group consisting of a G-protein coupled receptor gene, a kinase gene, a phosphatase gene, an ion channel gene, a nuclear receptor gene, an oncogene, a cancer suppressor gene, a viral receptor, a bacterial receptor gene, a P450 gene ~~gene~~, an insulin receptor gene, an immunoglobin gene, a metabolic pathway gene, a transcription factor gene, [[,]] a cytokine gene, a cell signaling pathway gene and a cell cycle gene.

33. (Original) The method of claim 25, wherein the third DNA construct is a bacterial artificial chromosome.

34. (Original) The method of claim 25, wherein the human DNA sequence is a human gene sequence having at least one intron contained therein.

35. (Previously Presented) The method of claim 34, wherein the third DNA construct has a selection marker contained within the at least one intron.

36. (Original) The method of claim 35, wherein the selection marker is added following the recombining step.

37. (Original) The method of claim 35, wherein the selection marker is a positive selection marker.

38. (Previously Presented) The method of claim 35, wherein the third DNA construct has a second selection marker that flanks the first or the second non-human animal DNA sequence.

39. (Currently Amended) The method of claim 25, wherein the human DNA sequence of the first DNA chimeric construct comprises a coding sequence comprising a start codon having a 5' end, and wherein the first non-human DNA sequence the first chimeric construct ~~in the second construct~~ is joined to the human DNA coding sequence at the 5' end of the start codon.

40. (Currently Amended) The method of claim 39, wherein the human DNA sequence of the second chimeric DNA construct comprises a coding sequence comprising[[es]] a stop codon having a 3' end, and wherein the ~~second~~ non-human DNA sequence of the second chimeric DNA construct ~~in the second construct~~ is joined to the 3' of the stop codon.

41. (Currently Amended) A humanized mouse produced by the method of claim 1, wherein the human DNA sequence is a gene selected from a G-protein coupled receptor gene, a kinase gene, a phosphatase gene, an ion channel gene, a nuclear receptor gene, an oncogene, a cancer suppressor gene, a viral receptor gene, a bacterial receptor gene, a P450 gene, an insulin receptor gene, an immunoglobin gene, ~~a metabolic pathway gene,~~ a transcription factor gene, [[,]] a cytokine gene~~, a cell signaling pathway gene~~ and a cell cycle gene.

Claim 42-43. (Canceled)

44. (Currently Amended) The humanized mouse of claim 41, wherein the gene is a PXR, [[,]] RXR, CYP3A4, CYP2B6, CYP2C9 or MDR1 gene.

45. (Currently Amended) A method of generating a humanized cell, comprising:

recombining a first DNA construct with a second DNA construct,

wherein the first DNA construct has a non-human animal DNA sequence contained therein, and

wherein the second DNA construct has a human DNA sequence contained therein ~~and the human DNA sequence is flanked by a first and a second non-human animal DNA sequence~~,

wherein the first and second ~~non-human animal DNA~~ constructs ~~sequences are from the same species,~~

~~wherein the first and second non-human animal DNA sequences are orthologous to and~~ have the same order and orientation relative to the human DNA sequences ~~as human sequences flanking the human DNA sequence~~ when ~~it is~~ present in the genome of a human;

a) generating at least two recombinant chimeric ~~isolating an intermediate homologously recombined third~~ DNA constructs comprising ~~having a the~~ human and non-human animal DNA sequences ~~flanked by~~ of the first and second ~~non-human animal~~ DNA constructs, wherein each

chimeric DNA construct comprises human DNA at one end of the chimeric DNA construct and non-human animal DNA at the other end of the chimeric DNA construct, and wherein a first chimeric DNA construct of the at least two recombinant chimeric DNA constructs comprises 5' regulatory DNA sequences and a second chimeric DNA construct of the at least two recombinant chimeric DNA constructs comprises 3' regulatory DNA sequences ~~and recombining the intermediate homologously recombined DNA construct with a third construct that has a mouse DNA sequence contained therein thereby generating a fourth DNA construct having a human sequence flanked by mouse sequences~~;

b) ligating the ends of the human DNA comprising the at least two chimeric DNA constructs;

c) recombining the ligated chimeric DNA constructs of step (b) with the second DNA construct to produce a third DNA construct, wherein the third DNA construct comprises human sequences of the second DNA construct flanked by non-human animal sequences of the first DNA construct; and

d) introducing the recombined third ~~fourth~~ DNA construct into a non-human animal cell of the same species as the non-human animal DNA sequences of the first ~~and second~~ construct[[s]], thereby generating a humanized cell.

46. (Previously Presented) The method of claim 45, wherein the non-human animal cell is a mouse embryogenic stem cell.

47. (Currently Amended) A PCR assembled DNA construct for performing homologous recombination within a cell of a non-human animal, the construct comprising:

a human DNA coding sequence having at least one intron disposed therein;

a selection marker gene contained within said at least one intron;

a first non-human animal DNA sequence and a second non-human animal DNA sequence,

wherein said first and second non-human animal DNA sequences flank the human DNA coding sequence,

wherein the first and second non-human animal DNA sequences are from the same species,

wherein the first and second non-human animal DNA sequences are orthologous to and have the same order and orientation relative to the human DNA sequence as human sequences flanking the human DNA sequence when it is present in the genome of a human; and

a second selection marker adjacent to one of the non-human DNA sequences,

wherein the construct is a bacterial artificial chromosome.

48. (Previously Presented) The DNA construct of claim 47, wherein the construct is a linearized bacterial artificial chromosome.

49. (Previously Presented) The DNA construct of claim 47, wherein the first and second non-human DNA sequences are mouse genomic DNA sequences.

50. (Previously Presented) The DNA construct of claim 47, wherein the non-human animal DNA sequences are from about 0.1 to 200 kb in length.

51. (Previously Presented) The DNA construct of claim 47, wherein the human DNA sequence comprises a coding sequence comprising a start codon having a 5'end and the first non-human sequence is joined adjacent to the 5' end of the start codon of the human DNA coding sequence.

52. (Previously Presented) The DNA construct of claim 51, wherein the human DNA coding sequence comprises a stop codon having a 3' end and the first non-human sequence is joined adjacent to the 3' end of the stop codon of the human DNA coding sequence.